Decision Memo for Ferrlecit®: Intravenous Iron Therapy (CAG-00046N)

Decision Summary

HCFA conducted a thorough review of the issue. The clinical evidence on IV iron therapy points to a significant benefit in the treatment of iron deficiency and anemia in Medicare's ESRD population, and therefore the overall clinical management of these patients. Moreover, as described above, the DOQI guidelines include specific recommendations related to the administration of supplemental iron. One of these guidelines notes that most hemodialysis patients will require IV iron on a regular basis.

One of the goals of HCFA is to promote improvements in the quality of care that is furnished to Medicare beneficiaries. For the past several years, HCFA has engaged in rigorous efforts to monitor and improve the management of anemia among ESRD patients. As part of the ESRD Clinical Performance Measures Project (CPMP), formerly known as the Core Indicator Project, HCFA gathers data on several anemia management indicators including hematocrit and hemoglobin levels on a national random sample of ESRD patients. Through the Scope of Work of their current contract, ESRD Networks are charged with developing and implementing special projects to assist ESRD facilities in the management of anemia. One such project is the clinical quality improvement (CQI) initiative identified by the CPMP to monitor and increase use of parenteral iron in anemia management.[10] As discovered by the ESRD Core Indicators Workgroup, in 1997 nearly 100% of ESRD patients were prescribed EPO in some form, yet only 50% were prescribed parenteral iron despite supportive reimbursement mechanisms, DOQI recommendations, and low incidence of adverse reactions.[11] Many believe that practitioners may be reluctant in prescribing iron dextran due to the unpredictable potential of life-threatening anaphylaxis. The CPMP is working towards implementing CQI strategies to improve parenteral iron prescription practices in ESRD facilities.

As discussed in Macdougall (1999), there are no randomized clinical trials that compare the safety and effectiveness of iron dextran and sodium ferric gluconate (IV iron products currently in use in the United States) to each other. The evidence suggests that there is little to distinguish these forms of IV iron therapy in terms of effectiveness. Rather, the medical literature indicates that the *mode* of intravenous administration is perhaps the most effective treatment for iron deficiency (both functional and absolute) in hemodialysis patients. Unlike oral iron products which must be absorbed through the GI tract, IV iron products are infused directly into the bloodstream in a form that is readily available to the bone marrow for RBC synthesis, resulting in an earlier correction of iron deficiency and anemia. The true distinction among these IV iron products lies within their safety profiles. Sodium ferric gluconate products have demonstrated no life-threatening anaphylaxis and a less severe adverse-reaction rate when compared to iron dextran products.[12] In fact, evidence suggests that the dextran component itself is what triggers the severe, life-threatening anaphylactic reactions often associated with IV iron dextran products.[13] Despite the potential dangers of IV iron dextran, there are some populations for whom this form of IV iron treatment is preferable. Unlike sodium ferric gluconate, iron dextran is a large and stable complex which can be administered to patients in large doses with low toxicity resulting from transient iron overload. The stability of the dextran complex allows total-dose infusions of more than one gram of iron in a single dialysis session. This aspect of IV iron dextran can be useful in hemodialysis patients who have fewer than three sessions per week or who are undergoing home dialysis.

Therefore, consistent with this agency's position of promoting efficient and effective anemia management practices for the ESRD population, HCFA will issue a positive national coverage determination for *sodium ferric gluconate complex in sucrose injection* for either first or second line treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoeitin therapy.

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Decision Memo

To:	File: Ferrlecit® (Intravenous iron replacement therapy for hemodialysis patients) CAG–00046N
From:	
	Hugh F. Hill III, MD, JD Acting Director, Coverage and Analysis Group
	Svati B. Patel Health Insurance Specialist, Coverage and Analysis Group
Re:	National Coverage Policy Request
Date:	April 20, 2000

This memorandum serves four purposes: (1) describes the etiology of iron deficiency in end stage renal disease (ESRD) patients and treatments currently available; (2) outlines Medicare's approach to drug coverage; (3) analyzes relevant clinical literature; and (4) delineates the reasons supporting a positive national decision to cover *sodium ferric gluconate complex in sucrose injection*.

Description and Background of the Treatment of Iron Deficiency in ESRD Patients

Iron deficiency is a common condition in ESRD patients undergoing hemodialysis. Iron is a critical structural component of hemoglobin, a key protein found in normal red blood cells (RBCs) which transports oxygen. Without this important building block, anemic patients experience difficulty in restoring adequate, healthy RBC (hematocrit) levels. A healthy individual has about 4-6 grams of iron in the body. On average 1-2 mg of iron enter and leave the body each day. More than two thirds of the body's total iron content is found within hemoglobin molecules.[1] Most of the remaining (non-hemoglobin) body iron is found in the form of ferritin or hemosiderin and stored in the liver, spleen, and bone marrow reticuloendothelial cells.

Iron deficiency occurs in ESRD patients for several reasons. Surgery, inflammatory responses, decreased dietary intake (due to low protein diets) and gastrointestinal absorption of iron (due to prescribed phosphate binders and chronic uremia itself) can deplete body iron stores. In addition, blood loss—due to repeated laboratory blood testing, needle punctures, shunt revisions, retention in dialyzer, platelet dysfunction, and use of anticoagulants—can be another possible cause of iron loss. Hemodialysis patients typically lose up to 15 ml to 25 ml of whole blood at each dialysis session. Chronic blood loss can lead to yearly losses of up to 6-8 grams of iron. In addition, using recombinant human erythropoietin (EPO) therapy to correct anemia in ESRD patients can further exhaust body iron stores. Normally functioning kidneys produce the hormone erythropoietin to stimulate the production of RBCs (a process known as erythropoiesis) if levels drop below normal. In ESRD patients where anemia is common and erythropoietin production is impaired, synthetic EPO therapy is sometimes used to help increase hematocrit levels. However, administering EPO increases iron use in the body, which in turn further strains iron stores that are already quite low. Patients with iron deficiency become unresponsive to EPO therapy because the body can not produce healthy RBCs without adequate levels of iron. The importance of correcting anemia and maintaining adequate hematocrit and hemoglobin levels has been well documented. Studies have shown that lower hematocrit levels can increase the risk of mortality and hospitalization.[2,3] Increasing hematocrit levels to a range of 33% to 36% can improve patient survival and quality of life. In order to maximize responsiveness to EPO, anemic ESRD patients must be monitored and treated for iron deficiency.

Iron deficiency, especially in ESRD patients undergoing EPO therapy and hemodialysis, can manifest itself in two ways: absolute iron deficiency and functional iron deficiency. Absolute iron deficiency occurs when body iron stores are severely depleted and erythropoiesis is impeded due to a lack of available iron for hemoglobin synthesis. Diagnosis of absolute iron deficiency is made when serum ferritin levels (a measure of body iron stores) are less then 100-ng/ml and percent transferrin saturation (a measure of the availability of iron for erythropoiesis) is less then 20%. In contrast, functional iron deficiency occurs when the rate of iron release from body stores, which would ordinarily be adequate to meet the needs of normal erythropoiesis, is not adequate to meet the needs of EPO-stimulated erythropoiesis. In functional iron deficiency, the increased need for iron (brought on by EPO) to support hemoglobin synthesis is greater than what can be released from body iron stores. This can occur in spite of adequate body iron stores. Iron is transported to the bone marrow for RBC synthesis by a serum protein called transferrin. Many researchers theorize that, under EPO stimulation, the transport of iron by transferrin molecules to the marrow may be a rate-limiting step in the process of erythropoiesis. This theory is supported by the fact that iron deficiency has been documented in patients who would otherwise be considered iron-replete.[4] An inadequate iron supply to the bone marrow can impair a patient's response to EPO, which can occur regardless of adequate body iron stores. Functional iron deficiency is suspected in patients with percent transferrin saturation less than 20% even with adequate serum ferritin levels.

Nearly 90% of ESRD patients will require iron supplementation at some point during their treatment.[5] Clinical management of iron deficiency involves treating patients with iron replacement products while they undergo hemodialysis. Body iron stores can be supplemented with either oral or intravenous (IV) iron products. There are several products currently approved by the Food and Drug Administration (FDA) for the treatment of iron deficiency in ESRD patients. Oral iron is generally used as a first-line therapy option in treating iron deficiency. Oral iron salts are available in liquid or tablet form and are taken two to three times per day. Oral iron supplementation has several disadvantages that include side effects, poor compliance, poor absorption, and low efficacy. Gastrointestinal (GI) side effects include constipation, nausea, vomiting, and gastritis and can occur in up to 20% of patients. Although these side effects are often the cause of poor compliance, studies show that even with strictly enforced compliance oral iron is still ineffective in treating iron deficiency in ESRD patients. Only about 1-2 mg of iron normally enters the body each day through the intestine. There is evidence that shows that iron absorption in the GI tract is hindered in the presence of certain medications (such as phosphate binders), poor consumption of iron containing foods (due to restricted, low-protein diets), and chronic uremia.[6,7] Slow absorption from the GI tract prevents timely repletion of body iron stores which is necessary in ESRD patients undergoing EPO therapy. It has been suggested that most patients taking oral iron will not respond to the treatment.[8] Currently, there is no evidence that defines specific populations that will and will not effectively respond to oral iron therapy.

Since iron supply may be a rate-limiting step in the process of erythropoiesis, the rationale for using IV iron is that it can be infused directly into the blood stream and readily available to the bone marrow. The two IV iron products, both iron dextran, previously on the market in the United States are indicated for use as second-line therapy after patients fail oral iron therapy. They are considered second line treatment options because iron dextran products have demonstrated a small incidence (0.7%) of severe, life-threatening anaphylaxis. These type I hypersensitivity reactions, which are not dose-related, are immunoglobulin (Ig) E-mediated and are apparently exclusively associated with the dextran forms of injectable iron. A second class of adverse reactions that are considered less severe includes symptoms such as breathless, wheezing, abdominal or back pain, nausea, vomiting, and hypotension. These reactions, which are dose-related and not exclusive to dextran products, are largely due to an overload of the transferrin molecule by administration of large doses of IV iron resulting in small amounts of ionized "free" iron remaining in the bloodstream. Excessive IV iron overload carries the risk of hemosiderosis, hepatic or cardiac organ dysfunction (from excess iron deposition), and bacterial infection.

Recent Developments

In August 1999, the Health Care Financing Administration (HCFA) received a formal coverage request from Schein Pharmaceutical, Inc. for Ferrlecit®, its new injectable iron product. Ferrlecit® (*sodium ferric gluconate complex in sucrose injection*) is an IV iron product that was approved by the FDA on February 18, 1999. It is indicated for "the treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental EPO therapy".[9] No other limitations were placed on its use as either first or second line therapy option. Ferrlecit® contains no dextran polysaccharides and can thus serve as an alternative to patients who exhibit dextran sensitivity. Due to its FDA indications, this product is also considered an alternative to oral iron therapy as a first line therapy option. Schein Pharmaceutical, Inc. requested coverage of Ferrlecit® for the treatment of iron deficiency for those patients who fall under the FDA approved indication. In need of additional evidence on IV iron therapies, HCFA posted the following policy-related questions to its website on January 26, 2000, and requested public input:

1. Is there any evidence that shows that sodium ferric gluconate is safer then oral iron therapy? Is there any evidence that shows sodium ferric gluconate is not riskier then oral iron?
2. What is the evidence that sodium ferric gluconate is more effective than oral iron or can a population be defined for which this is so? What is the added value of IV iron as a first-line therapy option without a trial of oral iron?
3. Is there a definable subset of anemic ESRD patients who should not be tried on oral iron before parenteral iron?
4. What is the evidence supporting the statement made in the normal request that "patients with functional iron deficiency do not meet laboratory criteria for absolute iron deficiency, but demonstrate an increase in hemoglobin/hematocrit or a decrease in EPO dosage with stable hemoglobin/hematocrit when parenteral iron is administered"?

Both Schein Pharmaceutical, Inc. and American Regent Laboratories, Inc. responded to HCFA’s request with additional evidence regarding IV iron therapies. All materials submitted were reviewed in preparation of this memorandum. We note that American Regent Laboratories, Inc. submitted material on IV iron sucrose products, in light of pending FDA-approval later this year. We have notified them that they should apply for a national coverage review once FDA has approved their particular drug.

National Kidney Foundation-Dialysis Outcomes Quality Initiative: Practice Guidelines

In March of 1995, the National Kidney Foundation-Dialysis Outcomes Quality Initiative (NKF-DOQI) was established with the primary objective of improving patient outcomes and survival by recommending optimal clinical practices through the development of evidence-based practice guidelines. One of the clinical areas the DOQI workgroups focused on was anemia management and the role of iron supplementation. The following five issues were raised by the Anemia Work Group:

1. Iron (blood) losses are high, particularly in the hemodialysis patient.
2. Oral iron usually cannot maintain adequate iron stores, particularly in the hemodialysis patient treated with EPO.
3. EPO, by stimulating erythropoiesis to greater than normal levels, often leads to functional iron deficiency.
4. Prevention of functional (and absolute) iron deficiency by regular use of intravenous iron (i.e., small doses, weekly, to replace predicted blood losses) improves erythropoiesis.
5. The serum iron, total iron binding capacity, and serum ferritin are the best indicators of iron available for erythropoiesis and iron stores, but do not provide absolute criteria of either iron deficiency or iron overload.

A review of the medical evidence pointed to the inadequacy of oral supplementation in maintaining adequate body iron stores. The Work Group acknowledged that, although there may be some temporary improvements in hematocrit and hemoglobin levels with oral iron therapy, the rate of iron loss greatly exceeds the rate of GI absorption and ultimately body iron stores will become depleted. Most ESRD patients will eventually need IV iron treatment to replenish body iron stores. The evidence on IV iron has shown significant improvements in EPO response as well as hemoglobin and hematocrit levels. A number of studies also point to significant reductions in the amount of EPO required to maintain adequate hemoglobin and hematocrit levels in patients undergoing IV iron therapy. After careful review of the clinical evidence, the Anemia Work Group recommended regular amounts of IV iron therapy in patients receiving EPO based on the following rationale:

1. Erythropoiesis requires both iron and erythropoietin.
2. Oral iron fails to maintain adequate iron stores in most hemodialysis patients, resulting in persistence of moderate anemia, which increases morbidity and mortality.
3. The use of IV iron will increase hematocrit and hemoglobin levels, and therefore improve morbidity and survival in chronic renal failure patients.
4. The health benefits of IV iron are expected to exceed its adverse effects resulting in a net health benefit

Evidence of Clinical Effectiveness

The packages of materials submitted by Schein Pharmaceuticals, Inc. and American Regent Laboratories, Inc. demonstrate the medical effectiveness of IV iron as a treatment option for iron deficiency in anemic ESRD patients. The particular studies mentioned below address safety and efficacy concerns as well as comparability to oral iron products currently used by practitioners.

- Nissenson, *et al.* (1999) conducted a North American multi-center clinical trial that looked at the safety and effectiveness of sodium ferric gluconate and its comparability to other modes of iron therapy. Eighty-eight patients undergoing hemodialysis and EPO therapy were randomized into either a high-dose (1000mg) or a low-dose (500mg) iron therapy group. These randomized groups were compared to a historically matched control group receiving only oral iron supplementation. The high-dose iron group showed significantly better improvements in hemoglobin and hematocrit levels when compared to both the low-dose and oral iron groups. There were no significant differences between the low-dose group and the historical controls. There were no adverse events reported that could be definitively linked to sodium ferric gluconate. Most events were mild or moderate in severity and were not dose-related. The concern with this study is the lack of comparison between comparable modes of iron treatment. IV iron dextran products were not used as a control comparison group. However, the study provides persuasive evidence that suggests that sodium ferric gluconate is more effective that oral iron therapy.

- Faich and Strobos (1999) reviewed claims data in their international analysis on the safety of IV sodium ferric gluconate as compared to IV iron dextran therapy. Researchers developed safety profiles of the two forms of IV iron therapy using allergic adverse event reports collected by the World Health Organization (WHO), German Health Bureau, United States, and manufacturers. The number of adverse events was compared to the volume of iron products sold within the United States and Europe. Allergic reaction rates were calculated: 3.3 allergy episodes per million doses per year for sodium ferric gluconate compared to 8.7 allergy episodes per million doses per year for iron dextran. In looking at case fatality rates (number of deaths resulting from adverse events per total number of adverse events), iron dextran had a rate of 15.8% while sodium gluconate reported no deaths. The methods used to calculate these rates raise concerns about the reliability of cross-cultural comparisons. Standards of medical practice for ESRD are not consistent between countries. For example, reporting practices for adverse events may vary from one country to another. In addition, the United States market is solely dominated by iron dextran therapy, whereas the European markets utilize a variety of non-dextran IV iron products. Finally, although the study attempts to distinguish between safety profiles, the comparable effectiveness of one IV iron product to another is not reflected in the data.

- Macdougall, *et al.* (1996) examined the effectiveness of IV iron dextran compared to both oral iron supplementation and no iron supplementation over a period of four months in a prospective randomized controlled study on iron-replete patients (serum ferritin levels 100 – 800 µg/liter) receiving EPO therapy. Thirty-eight patients were enrolled into the study protocols. One patient was excluded from the study due to a mild anaphylactoid reaction during his first infusion of IV iron. The remaining thirty-seven patients were randomized into the following groups: IV iron therapy (n=12), oral iron therapy (n=13), and no iron treatment (n=12). At the end of the study, the IV iron group showed significantly greater increases in hemoglobin levels compared to the other two groups. There were no significant differences in hemoglobin response between the oral iron and no iron groups at any time during the study. Furthermore, whereas serum ferritin levels remained fairly constant in the IV iron group, both the no iron and oral groups showed a progressive and significant decrease in body iron stores compared to the IV iron group. Although there is cause for concern regarding the small number of patients in each group (which could affect the results by introducing selection bias), this study provides persuasive evidence regarding the increased effectiveness of IV iron dextran over either oral iron therapy or no iron therapy. It is interesting to note that the oral iron treatment group did not at any point in the study show significantly better improvements in hemoglobin and serum ferritin levels compared to the control group. The drop in serum ferritin levels in the oral iron group suggests that this treatment modality may be inadequate in maintaining sufficient iron stores.

- Sunder-Plassmann and Hörl (1999) reviewed the available clinical evidence on the comparative safety, toxicity, pharmacology, and effectiveness of the three IV iron agents currently in use throughout the world: iron dextran, iron sucrose, and sodium ferric gluconate. The authors found all three therapies to be highly effective in treating iron deficiency and improving a patient's response to EPO. Although all three therapies were considered efficacious, there were differences in regards to safety. IV iron dextran was found to be the least attractive when compared to iron sucrose and sodium ferric gluconate products. This conclusion was largely due to the life-threatening anaphylactic reactions that have been found to occur in a small number of patients treated with iron dextran. Despite better safety profiles, the authors recommended that iron sucrose and sodium ferric gluconate be administered to patients in low doses because of evidence that points to dose-related non-life threatening adverse reactions such as flushing, hypotension, and nausea. It is theorized that such reactions occur due to the transient overload of the transferrin molecule. These symptoms of iron overload have often been mitigated by administration of lower doses of the intravenous preparation.

For a complete analysis of all scientific material submitted, please refer to the literature review chart and bibliography attached to this memorandum.

National Coverage Decision

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1 Andrews (1999)
2 Ma, *et al*. (1999)
3 Xia, *et al*. (1999)
4 Hussain, *et al*. (1998)
5 Macdougall (1999)
6 Silverberg, *et al*. (1996)
7 Kooistra, *et al*. (1998)
8 National Kidney Foundation (1997)
9 FDA labeling
10 Owen, *et al*. (1999)
11 Frankenfield, *et al*. (2000)
12 Bailie, *et al*. (2000)
13 Faich, *et al*. (1999)

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